REMARKS

The Office Action sent March 19, 2009 has been received and reviewed. All claims currently under consideration stand rejected. All amendments and cancellations are made without prejudice or disclaimer. Support for the current amendments and new claims can be found throughout the as-filed Specification, for example, in at least paragraphs **[0019], [0021]-[0022], [0038], [0040], [0041], [0048]-[0052],** and the claims as previously presented. Accordingly, applicants submit that no new matter has been added. Reconsideration is respectfully requested.

Claim Objection

Claim 2 stands objected to for a typographical error. Claim 2 has been canceled.

Double Patenting

Claims 1-2, 4-7, 12-13, and 20-24 stand provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1, 2, 11-14, 18-25, 29, 33-38, 40-52, 56-59, 61, and 65-66 of co-pending U.S. Application No. 11/407,103 (hereinafter '103). Specifically, the Office alleges that although the conflicting claims are not identical, they are not patentably distinct from each other because the compositions and methods of treatment claims of '103 recite a composition that comprises a vaccine directed against TGF-alpha, where the TGF-alpha is coupled to a carrier protein such as P64K. Office Action, page 3. The Office further alleges that a preferred embodiment appears to be human TGF-alpha since the specification teaches an example of the use of TGF-alpha as a vaccine for making ligand blocking antibodies for use in patients. *Id.* Claims 2, 7, and 20 have been canceled, thus rendering the provisional rejection of those claims moot. Applicants respectfully traverse the provisional rejection of the remaining claims.

Independent claim 1 has been amended to recite, in part, a composition comprising: a fusion protein between human TGFα and P64k; and human EGF; and an adjuvant. Claims 21-24 have been amended to depend from claim 1 rather than claim 20. Applicants note that the claims of co-pending '103 are directed to an immunotherapy combination comprising a) an antibody against an RTK receptor, and b) a vaccine which induces antibodies against a ligand of an RTK

receptor (underlining added) which provides a combination of passive and active immunotherapy. The composition claims of the present application do not include an antibody against an RTK receptor. Furthermore, the co-pending application does not include claims which combine a fusion protein between human TGFα and P64k and human EGF.

In view of the present claim amendments, it is respectfully submitted that there is no overlapping subject matter between the claims of the present application and co-pending '103. Reconsideration and withdrawal of the provisional rejection are respectfully requested.

Claims Rejections – 35 U.S.C. § 112

Claims 23 and 24 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office alleges that the claims contain new matter. Specifically, the Office alleges while the Specification describes different doses of hTGFα and different amounts of adjuvants, there does not appear to be support for the specific ratios as recited in the claims. *Id.* at 4. The Office further asserts that applicants failed to specifically point out support for the previously claimed subject matter. *Id.* Applicants respectfully traverse the rejection.

Applicants respectfully reference the response submitted October 1, 2008, wherein it is stated "[s]upport for the current amendments and new claim can be found throughout the Specification, for example, in paragraphs **[0040], [0056], [0085], [0087]-[0090]**." Paragraphs **[0086]-[0087]** describe a composition containing .6 mg of protein in 2 mg of adjuvant. Applicants' as-filed Specification, paragraphs **[0086]-[0087].** Similarly, paragraph **[0090]** describes a composition containing 50 μg of protein in 2 mg of adjuvant. *Id.* at **[0090].** These described compositions have a ratio of the adjuvant to the hTGFα of about 3 to 1 by weight (.6 mg in 2 mg of adjuvant) and about 40 to 1 by weight (50 μg of protein in 2 mg of adjuvant), respectively. These values can be readily calculated as the molecular ratio based on the concentration of the compositions described in the Specification. Furthermore, a person of ordinary skill in the art would readily recognize that these values are, at the very least, implicit in the above referenced paragraphs.

Applicants note that rephrasing of passages in the Specification does not constitute new

matter. *See, e.g.,* MPEP § 2163.07. The claimed ratios are tantamount to a rephrasing of the compositions as described by the Specification, and thus should not constitute new matter. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim Rejections – 35 U.S.C. § 103

Claims 1-2, 7, 12, and 20-21 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hoeprich (of record) in view of Davila (US Patent 5,894,018) and further in view of Rodriquez et al. (US Patent 5,286,484). Specifically, the Office alleges that a person of ordinary skill in the art would be motivated to combine the teachings of Hoeprich, Davila, and Rodriguez to make a TGFα-P64k conjugate and would reasonably expect such conjugate would be immunogenic. Office Action, page 7. The Office further alleges that Hoeprich teaches compositions where hTGFα is present at 50-200 micrograms per dose. *Id.* Claims 2, 7, and 20 have been canceled, thus rendering the rejection of those claims moot. Applicants respectfully traverse the rejection of the remaining claims.

While applicants do not agree with the Office's assertions, claim 1 has been amended to recite, in part, a composition comprising: a fusion protein between hTGFα and P64k, hEGF, and an adjuvant. In an exemplary embodiment, the claimed composition is useful for the vaccination of cancer patients for the treatment of epithelial cancers responsive to hTGFα or hEGF. None of the references relied upon by the Examiner discloses a fusion protein between hTGFα and P64k which is useful for an anti-EGF and an anti-TGFα antibody response. Furthermore, none of references discloses a fusion protein between hTGFα and P64k with hEGF and an adjuvant useful for the treatment of epithelial cancers responsive to EGF and/or TGFα.

To establish a *prima facie* case of obviousness the prior art reference (or references when combined) **must teach or suggest all the claim elements**. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974); *see also* MPEP § 2143.03. Additionally, there must have been "a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 399, 82 USPQ2d 1385, 1396 (2007). Furthermore, to establish a *prima facie* case of obviousness there must have been a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). Finally, the reason that would have prompted the combination and the reasonable

expectation of success must be found in the prior art, common knowledge, or the nature of the problem itself, and not based on the applicant's disclosure. *DyStar Textilfarben GmbH & Co. Deutschland KG v. C. H. Patrick Co.*, 464 F.3d 1356, 1367 (Fed. Cir. 2006); MPEP § 2144.

None of the references relied upon by the Office, either alone or in combination, discloses, teaches, or suggests the presently claimed composition. For example, Hoeprich teaches that TGFα plays an important role in cellular growth mechanisms and that the mitogenic effects of TGFα are mediated through EGF receptors. Hoeprich only identifies immunodominant regions of TGFα. There is no teaching or suggestion of a composition comprising a TGFα-P64k fusion protein and EGF and an adjuvant.

Similarly, Davila does not teach or suggest the claimed composition. Davila teaches the use of EGF chemically conjugated with a carrier protein for treatment of EGF dependent malignant diseases and is silent with respect to TGFα. Davila does not teach or suggest a composition comprising EGF peptides without the use of a carrier protein and a second growth factor (*e.g.*, TGFα) coupled to a carrier protein. Nor does Davila teach or suggest the use of multiple and distinct factors and/or fusion proteins, as presently claimed.

Rodriquez is silent with respect to TGFα or EGF. Rather, Rodriquez merely provides information with regard to P64k.

In view of the fact that the combined references do not teach or suggest all the elements of the amended claims, claims 1, 12, and 21 are not obvious over Hoeprich, Davila, and Rodriquez.

Applicants additionally submit the amended claims are not obvious as none of the references expressly or inherently teaches or suggests any combinations or modifications in accordance with applicants' claimed composition. While applicants acknowledge that express motivation in prior art references is not necessarily required, "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless **>the results would have been predictable to one of ordinary skill in the art." MPEP § 2143.01 citing *KSR International Co. v. Teleflex Inc.*, 550 U.S. at 401, 82 USPQ2d at 1396 (2007).

Even if a person ordinary skill in the art would have been motivated to prepare a fusion protein between hTGFα and P64k, which applicants dispute, the person of ordinary skill would not have reasonably predicted that a composition comprising a fusion protein between hTGFα

and P64k, EGF, and an adjuvant would be useful for the treatment of EGF responsive epithelial cancers. As noted in previous responses, Hoeprich discloses that TGFα shares only 33-40% sequence homology with EGF and that their antibodies do not cross-react and differ significantly in their occurrence. Office Action at 6. Furthermore, as discussed at paragraph **[0018]** of the description, previous studies have shown that vaccination with TGFα elicited levels of anti-EGF antibodies which were insufficient to generate an effective EFG immunecastration response. Gonzalez also discloses that after immunization with the fusion protein EGF-p64K and the antibody response was not cross-reactive with TGFα in mice or in monkeys. This data, at the very least, suggests that the references teach away from a composition comprising both a hTGFα -P64k fusion protein and hEGF. Additionally, a person skilled in the art would not have a reasonable expectation of success for the use of a fusion protein between hTGFα and P64k either alone or in combination with EGF for the treatment of EGF responsive epithelial cancers and also TGFα responsive epithelial cancers.

In view of the present claim amendments and the preceding reasons, it is respectfully submitted that the subject matter of independent claim 1 and its dependent claims is not obvious in view of the Hoeprich, Davila, and Rodriquez. Reconsideration and withdrawal of the 35 U.S.C. § 103 rejections are respectfully requested.

Claims 1-2, 4-5, 12-13, and 20-21 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hoeprich in view of Davila, in view of Rodriquez, and further in view of Gonzalez-1997 (Vaccine Research, 6(2): 91-100, 1997). Claims 2 and 20 have been canceled, thus rendering the rejection of those claims moot. Applicants respectfully traverse the rejection of the remaining claims.

Applicants note the standards for obviousness as previously described and submit that the amended claims are not obvious over Hoeprich, Davila, Rodriquez, and Gonzalez-1997, as these combined references do not teach or suggest the claimed composition, to wit, a composition comprising: a fusion protein between hTGFα and P64k, hEGF, and an adjuvant.

As discussed in previous paragraphs, the combined references of Hoeprich, Davila, and Rodriquez do not teach or suggest the claimed composition. Gonzalez when combined with the other references of record do not teach or suggest a composition comprising both a fusion protein

between hTGFα and P64k and hEGF. Gonzalez teachings are directed to a fusion protein that contains human recombinant EGF. Furthermore, Gonzalez does not provide any evidence that a person of ordinary skill would have reasonably predicted that a composition comprising a fusion protein between hTGFα and P64k, EGF, and an adjuvant would be useful for the treatment of EGF responsive epithelial cancers.

Additionally, as previously asserted, the combined references, at the very least, teach away from a composition comprising both a hTGFα-P64k fusion protein and hEGF. (1) Previous studies have shown that vaccination with TGFα elicited levels of anti-EGF antibodies which were insufficient to generate an effective EFG immunecastration response and (2) Gonzalez discloses that after immunization with the fusion protein EGF-p64K and the antibody response was not cross-reactive with TGFα in mice or in monkeys. This evidence, at the very least, teaches away from a composition comprising both a hTGFα-P64k fusion protein and hEGF.

Applicants submit that claims 1, 4-5, 12-13, and 21 are not obvious over Hoeprich, Davila, Rodriquez, and Gonzalez-1997. Reconsideration and withdrawal of the 35 U.S.C. § 103 rejections are respectfully requested.

Claims 1-2, 4-7, 12-13, and 20-21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hoeprich in view of Davila, in view of Rodriquez, in view of Gonzalez-1997 and in further view of Ritzenthaler (General Virology, 76: 907-915, 1995). Claims 2, 7, and 20 have been canceled, thus rendering the rejection of those claims moot. Applicants respectfully traverse the rejection of the remaining claims.

Applicants note the standards for obviousness as previously described and submit that the amended claims are not obvious over Hoeprich Davila, Rodriquez, Gonzalez-1997, and Ritzenthaler, as these combined references do not teach or suggest the claimed composition, to wit, a composition comprising: a fusion protein between hTGFα and P64k, hEGF, and an adjuvant.

As discussed in previous paragraphs, the combined references of Hoeprich, Davila, Rodriquez, and Gonzalez-1997 do not teach or suggest the claimed composition. The teachings of Ritzenthaler, when combined with the other references of record, do not teach or suggest a composition comprising both a fusion protein between hTGFα and P64k and hEGF.

Furthermore, Ritzenthaler does not provide any evidence that a person of ordinary skill would have reasonably predicted that a composition comprising a fusion protein between hTGFα and P64k, EGF, and an adjuvant would be useful for the treatment of EGF responsive epithelial cancers.

As previously asserted, the combined references at the very least teach away from a composition comprising both a hTGFα -P64k fusion protein and hEGF. (1) Previous studies have shown that vaccination with TGFα elicited levels of anti-EGF antibodies which were insufficient to generate an effective EFG immunecastration response and (2) Gonzalez discloses that after immunization with the fusion protein EGF-p64K and the antibody response was not cross-reactive with TGFα in mice or in monkeys. This evidence, at the very least, teach away from a composition comprising both a hTGFα-P64k fusion protein and hEGF.

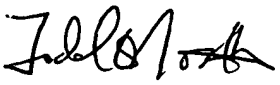
Applicants submit that claims 1, 4-5, 12-13, and 21 are not obvious over Hoeprich, Davila, Rodriquez, Gonzalez-1997, and Ritzenthaler. Reconsideration and withdrawal of the 35 U.S.C. § 103 rejections are respectfully requested.

Rejoinder

Applicants respectfully request rejoinder of claims 14-18. If an applicant elects claims directed to a product, and such claim is subsequently found allowable, withdrawn claims which depend from, or otherwise include all elements of the allowable product claim, will be rejoined. M.P.E.P. § 821.04; *see also In re Ochiai*, 71 F.3d 1565 (Fed. Cir. 1995); *In re Brouwer*, 77 F.3d 422 (Fed. Cir. 1996). Applicants submit that claim 1 is in condition for allowance. As such, applicants respectfully request the rejoinder of claims 14-18 which depend from or include all the elements of allowable claim 1.

In light of the foregoing amendments and remarks, claims 1, 4 -6, 12-13, 21-24, and new claims 25-26 are believed to be in condition for allowance. If questions remain after consideration of the foregoing, or if the Office should determine that there are additional issues which might be resolved by a telephone conference, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



Todd E. North
Registration No. 57,795
Attorney for Applicants
TRASKBRITT, P.C.
P.O. Box 2550
Salt Lake City, Utah 84110-2550
Telephone: 801-532-1922

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